Sir:

David Snowdon’s thought-provoking account of an elderly nun named Sister Mary, “Aging and Alzheimer’s Disease: Lessons From the Nun Study” in the February 1997 issue, concludes that individuals may be cognitively intact despite severe Alzheimer’s-type changes in the brain. His conclusion, based on Sister Mary’s apparent cognitive intactness at the time of her death at age 101, is doubtful.

The evidence for Sister Mary’s cognitive integrity was a Mini-Mental State Examination (MMSE) score of 27 out of a possible 30 points, a performance level equal to or higher than the average observed in her peers, and informal interviews with health care workers shortly before her death. However, Sister Mary’s Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) battery tests provide clear evidence of impairment by reference to normative data for the CERAD battery by age and education (Welsh et al., 1994). Even considering that Sister Mary was older than the normative reference group, her scores on naming, verbal fluency, learning, and memory were far below normal. Her delayed verbal recall retention rate of 50% is particularly diagnostic; such tasks have repeatedly shown their sensitivity to mild Alzheimer’s disease (Welsh, Butters, Hughes, Mohs, & Heyman, 1991) and their integrity in normal aging. Furthermore, Sister Mary’s naming performance of 9 out of a possible 15 falls well below expectation (the mean of normals typically ranges from 13 to 15) on this relatively insensitive derivation of the Boston Naming Test (Lansing, Randolph, Ivnik, & Cullum, 1996). Verbal category fluency, another measure sensitive to Alzheimer’s disease, was reduced. She was able to generate only 8 animal names in one minute. This is well below expectation, regardless of the norms used.

Regarding the contention that Sister Mary’s MMSE score was well above many of her contemporaries in the Nun Study, it should be noted that the use of an eighth grade educational reference point may over-estimate her level of functioning. Based on her accomplishments, Sister Mary was above average in terms of premorbid intellectual endowment; many older persons had to curtail schooling as a result of situational factors rather than lack of ability. Hence, among the oldest old in particular, large score adjustments for education may not be appropriate. Nevertheless, Sister Mary’s score on the MMSE falls in the normal range, regardless of norms used. The rationale for commenting that Sister Mary’s “predicted” MMSE score would be 4 out of 30 “based on her old age and low education” is an example of the dangers of extrapolation. Only severely demented or aphasic individuals obtain scores this low, and no “normal” functioning elderly individual familiar with the English language scores at such a level. Further a “normal” score on a simple screening test such as the MMSE cannot be equated with the absence of dementia. Such brief measures often fail to detect significant memory and/or visuospatial deficits; more detailed neuropsychometric evaluations may reveal significant impairments in the face of “normal” MMSE scores. The diagnosis of Alzheimer’s disease requires deficits in several cognitive domains that may not be adequately represented by brief cognitive screening tools.

Finally, the “informal interviews” with health care workers about Sister Mary before her death cannot be used to infer cognitive normality. It was noted that “standard” nursing reports indicated that she was still able to remember “a short list of items,” with no data or indication of what stimuli were used.

In short, Sister Mary had evidence of Alzheimer’s disease based on her cognitive performance. The neuropathologic findings of atrophy, plaques, and tangles are supportive, rather than surprising. The report that Sister Mary’s test scores were generally superior to those of the other sisters who had died further suggests that dementia was more widespread in this sample than perhaps had been recognized.

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Professor Snowdon replies:

The inspiring story of Sister Mary, a centenarian from the Nun Study, was included in an article (Snowdon, 1997) that was written to provoke discussion about the need to develop clinical and neuropathologic definitions of Alzheimer’s disease in the very old. Dr. Weiner and his colleagues have commented on this article and we are happy to respond.

Sister Mary had the neuropathologic hallmarks of Alzheimer’s disease, as evidenced by abundant senile plaques and some neurofibrillary tangles in her neo-

References


cortex; substantial degeneration of the brain, including atrophy of frontal, temporal, and parietal lobes of the neocortex; and an extremely low brain weight. Given the strong interaction between the neuropathologic lesions of Alzheimer’s disease and brain infarcts in “producing” dementia in our study population (Snowdon et al., 1997), we have suggested that Sister Mary may have been able to clinically compensate for the Alzheimer’s disease pathology because she was free of brain infarcts and other brain diseases.

Clinically, Alzheimer’s disease is noted by a progressive loss of cognitive abilities and the combination of a deficit in memory, a deficit in another area of cognition (such as language and visuospatial ability), and a deficit in social and daily functioning (American Psychiatric Association, 1994). Following these guidelines, we determined that Sister Mary was not demented based on a standard algorithm (which was not adjusted for age or education; Snowdon et al., 1997) that assesses performance on memory (i.e., the Delayed Word Recall test), tests of other areas of cognition, and performance on daily tasks.

During the year before her death, Sister Mary’s cognitive scores on the CERAD neuropsychological test battery (Morris et al., 1989) improved for some tests, showed no change for some tests, and slightly declined for others (Snowdon, 1997). Dr. Weiner and his colleagues are correct in stating that the Delayed Word Recall test is particularly sensitive to mild Alzheimer’s disease (Welsh et al., 1994). However, it is not correct to describe Sister Mary’s memory scores as being “far below normal.” In fact, her score of 5 on the Delayed Word Recall test is clearly above the score of 3 that is the cut point for impairment defined by Welsh and her colleagues. Sister Mary’s other memory test scores were lower, but still within normal limits.

Dr. Weiner and his colleagues seem to have made the assumption that the additional clinical information about Sister Mary included in the original article was used to make the determination that she was not demented. This information included her last MMSE score (which was 27 out of 30 and well within the normal range); the predicted MMSE score for the other sisters who died; and standard questionnaires completed by Sister Mary’s nurses during the last several days of her life. Rather than using this information as part of the diagnostic formula, we used it as supplemental material to aid in interpreting the cognitive test scores of a 101-year-old woman. The fact that Sister Mary was 30 years older than the average person included in the normative series currently available for the neuropsychological test battery (Welsh et al., 1994) underscores the need for additional consideration of the issues involved in interpreting the scores of very old individuals.

As described in the original article, Sister Mary did have what might be considered low scores on some cognitive tests (e.g., the Boston Naming Test and Verbal Fluency); we noted that these scores may reflect cognitive deficits attributable to the Alzheimer’s disease pathology seen in Sister Mary’s brain at autopsy. However, it is also possible that other factors, such as medical illness or sensory losses associated with advanced age, were partially responsible for these relatively low scores. For example, Sister Mary’s near visual acuity test scores (with her glasses on) were in the bottom decile of the distribution of scores for our population.

The phenomenal growth of the oldest segment of the general population lends a sense of urgency to the challenge to develop new criteria to help distinguish normal aging from dementia in very old individuals. While the population of the Nun Study is unique, its members, like Sister Mary, continue to challenge our view of what constitutes aging, disease, and normality in the very old.

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References